

(19) World Intellectual Property Organization
International Bureau



(43) International Publication Date
3 October 2002 (03.10.2002)

PCT

(10) International Publication Number
WO 02/076949 A1

- (51) International Patent Classification⁷: C07D 231/06, 401/04, A61K 31/415, A61P 25/00
- (74) Agent: MUIS, Maarten; OCTROOIBUREAU ZOAN B.V., P.O. Box 140, NL-1380 AC Weesp (NL).
- (21) International Application Number: PCT/EP02/03079
- (22) International Filing Date: 18 March 2002 (18.03.2002)
- (25) Filing Language: English
- (26) Publication Language: English
- (30) Priority Data:
01201062.5 22 March 2001 (22.03.2001) EP
- (71) Applicant (for all designated States except US): SOLVAY PHARMACEUTICALS B.V. [NL/NL]; C.J. Van Houtenlaan 36, NL-1381 CP Weesp (NL).
- (72) Inventors; and
- (75) Inventors/Applicants (for US only): LANGE, Josephus, H.M. [NL/NL]; c/o C.J. Van Houtenlaan 36, NL-1381 CP Weesp (NL). KRUSE, Cornelis, G [NL/NL]; c/o C.J. Van Houtenlaan 36, NL-1381 CP Weesp (NL). TIPKER, Jacobus [NL/NL]; c/o C.J. Van Houtenlaan 36, NL-1381 CP Weesp (NL). HOOGENDOORN, Jan [NL/NL]; c/o C.J. Van Houtenlaan 36, NL-1381 CP Weesp (NL).
- (81) Designated States (national): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW.
- (84) Designated States (regional): ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).
- Published:
— with international search report
- For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: 4,5-DIHYDRO-1H-PYRAZOLE DERIVATIVES HAVING CB₁-ANTAGONISTIC ACTIVITY

(57) Abstract: The present invention relates to a group of novel 4,5-dihydro-1H-pyrazole derivatives having S configuration at the 4-position of their 4,5-dihydro pyrazole ring which are potent antagonists of the cannabis CB₁-receptor. The compounds have the general formula (I) wherein- R and R₁ are the same or different and represent 3-pyridyl or 4-pyridyl or phenyl which may be substituted with halogen or methoxy, - R₂ and R₃ are the same or different and represent hydrogen, alkyl (1-3 C) or dimethylamino- R₄ represents phenyl which may be substituted with 1 or 2 substituents selected from the group halogen atoms, trifluoromethyl, methoxy and alkyl (1-3 C) and tautomers, prodrugs and salts thereof. These enantiomers are much more potent and selective antagonists of the cannabis CB₁-receptor, than the other enantiomer.

WO 02/076949 A1

4,5-Dihydro-1H-pyrazole derivatives having CB₁-antagonistic activity

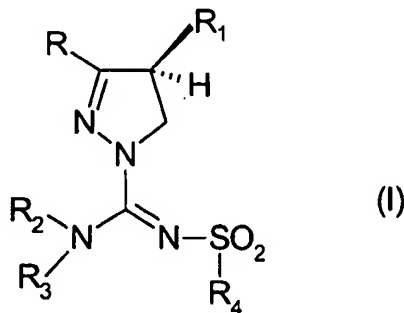
The present invention relates to a group of novel enantiomers of 4,5-dihydro-1H-pyrazole derivatives having S configuration at the 4-position of their 4,5-dihydropyrazole ring, to methods for the preparation of these compounds, and to pharmaceutical compositions containing one or more of these compounds as an active component.

The above mentioned (4S)-4,5-dihydro-1H-pyrazoles are potent Cannabis-1 (CB₁) receptor antagonists with utility for the treatment of psychiatric and neurological disorders.

Cannabinoids are present in the Indian hemp *Cannabis Sativa L.* and have been used as medicinal agents for centuries (Mechoulam, R.; Feigenbaum, J.J. *Prog. Med. Chem.* **1987**, *24*, 159). However, only within the past ten years the research in the cannabinoid area has revealed pivotal information on cannabinoid receptors and their (endogenous) agonists and antagonists. The discovery and the subsequent cloning of two different subtypes of Cannabinoid receptors (CB₁ and CB₂) stimulated the search for novel cannabinoid receptor antagonists (Munro, S.; Thomas, K.L.; Abu-Shaar, M. *Nature* **1993**, *365*, 61. Matsuda, L.A.; Bonner, T.I. *Cannabinoid Receptors*, Pertwee, R.G. Ed. **1995**, 117, Academic Press, London). In addition, pharmaceutical companies became interested in the development of cannabinoid drugs for the treatment of diseases connected with disorders of the cannabinoid system. The wide distribution of CB₁ receptors in the brain, in combination with the strictly peripheral localisation of the CB₂ receptor, makes the CB₁ receptor a very interesting molecular target for CNS-directed drug discovery in the areas of both psychiatric and neurological disorders (Consroe, P. *Neurobiology of Disease* **1998**, *5*, 534. Pop, E. *Curr. Opin. In CPNS Investigational Drugs* **1999**, *1*, 587. Greenberg, D.A. *Drug News Perspect.* **1999**, *12*, 458). Hitherto, three types of distinct CB₁ receptor antagonists are known. Sanofi disclosed their diarylpyrazole congeners as selective CB₁ receptor antagonists. A representative example is SR-141716A, which is currently undergoing Phase II clinical development for psychotic disorders (Dutta, A.K.; Sard, H.; Ryan, W.; Razdan, R.K.; Compton, D.R.; Martin, B.R. *Med. Chem. Res.* **1994**, *5*, 54. Lan, R.; Liu, Q.; Fan, P.; Lin, S.; Fernando, S.R.; McCallion, D.; Pertwee, R.; Makriyannis, A. *J. Med. Chem.* **1999**, *42*, 769. Nakamura-Palacios, E.M.; Moerschbaecher, J.M.; Barker, L.A. *CNS Drug Rev.* **1999**, *5*, 43). Aminoalkylindoles have been disclosed as CB₁ receptor antagonists. A representative example is Iodopravadoline (AM-630), which was introduced in

1995. AM-630 is a CB₁ receptor antagonist, but sometimes behaves as a weak partial agonist (Hosohata, K.; Quock, R.M.; Hosohata, Y.; Burkey, T.H.; Makriyannis, A.; Consroe, P.; Roeske, W.R.; Yamamura, H.I. *Life Sc.* **1997**, 61, PL115). More recently, researchers from Eli Lilly described aryl-aroyl substituted benzofurans as selective CB₁ receptor antagonists (e.g. LY-320135) (Felder, C.C.; Joyce, K.E.; Briley, E.J.; Glass, M.; Mackie, K.P.; Fahey, K.J.; Cullinan, G.J.; Hunden, D.C.; Johnson, D.W.; Chaney, M.O.; Koppel, G.A.; Brownstein, M. *J. Pharmacol. Exp. Ther.* **1998**, 284, 291). Recently, 3-alkyl-5,5'-diphenylimidazolidinediones were described as cannabinoid receptor ligands, which were indicated to be cannabinoid antagonists (Kanyonyo, M.; Govaerts, S.J.; Hermans, E.; Poupaert, J.H.; Lambert, D.M. *Biorg. Med. Chem. Lett.* **1999**, 9, 2233). Interestingly, many CB₁ receptor antagonists have been reported to behave as inverse agonists *in vitro* (Landsman, R.S.; Burkey, T.H.; Consroe, P.; Roeske, W.R.; Yamamura, H.I. *Eur. J. Pharmacol.* **1997**, 334, R1). Recent reviews provide a nice overview of the current status in the cannabinoid research area (Mechoulam, R.; Hanus, L.; Fride, E. *Prog. Med. Chem.* **1998**, 35, 199. Lambert, D.M. *Curr. Med. Chem.* **1999**, 6, 635. Mechoulam, R.; Fride, E.; Di Marzo, V. *Eur. J. Pharmacol.* **1998**, 359, 1).

It has now surprisingly been found that the novel enantiomers of 4,5-dihydro-1H-pyrazole derivatives having S configuration at the 4-position of their 4,5-dihydro pyrazole ring of the formula (I), prodrugs thereof, tautomers thereof and salts thereof



wherein

- R and R₁ are the same or different and represent 3-pyridyl or 4-pyridyl, or phenyl which may be substituted with halogen or methoxy,
- R₂ and R₃ are the same or different and represent hydrogen, alkyl (1-3 C) or dimethylamino
- R₄ represents phenyl which may be substituted with 1, 2 or 3 substituents selected from the group halogen, trifluoromethyl, methoxy and alkyl (1-3 C)

are much more potent and selective antagonists of the cannabis CB₁-receptor, than the correspondence R-enantiomer.

5 Due to the potent CB₁ antagonistic activity the compounds according to the invention are suitable for use in the treatment of psychiatric disorders such as psychosis, anxiety, depression, attention deficits, memory disorders and appetite disorders, obesity, neurological disorders such as dementia, distonia, Parkinson's
10 disease, Alzheimer's disease, epilepsy, Huntington's disease, Tourette's syndrome, cerebral ischaemia, as well as for the treatment of pain disorders and other CNS-diseases involving cannabinoid neurotransmission, and in the treatment of gastrointestinal disorders and cardiovascular disorders.

15 The affinity of the compounds of the invention for cannabinoid CB₁ receptors was determined using membrane preparations of Chinese hamster ovary (CHO) cells in which the human cannabis CB₁ receptor is stably transfected in conjunction with [3H]CP-55,940 as radioligand. After incubation of a freshly prepared cell membrane preparation with the [3H]-ligand, with or without addition of compounds of the invention, separation of bound and free ligand was performed by filtration
20 over glassfiber filters. Radioactivity on the filter was measured by liquid scintillation counting.

25 The cannabinoid CB₁ antagonistic activity of compounds of the invention was determined by functional studies using CHO cells in which human cannabinoid CB₁ receptors are stably expressed. Adenylyl cyclase was stimulated using forskolin and measured by quantifying the amount of accumulated cyclic AMP. Concomitant activation of CB₁ receptors by CB₁ receptor agonists (e.g. CP-55,940 or (R)-WIN-55,212-2) can attenuate the forskolin-induced accumulation of cAMP in a concentration-dependent manner. This CB₁ receptor-mediated response can
30 be antagonised by CB₁ receptor antagonists such as the compounds of the invention.

The invention relates both to the E isomer, Z isomer and E/Z mixtures of compounds having formula (I).

35 The compounds can be brought into forms suitable for administration by means of usual processes using auxiliary substances and/or liquid or solid carrier materials.

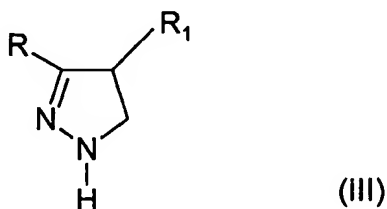
The compounds of the invention having formula (III) (*vide infra*) can be obtained according to methods known, for example: a) EP 0021506; b) DE 2529689.

A suitable synthesis for the racemic compounds according to the present invention is the following:

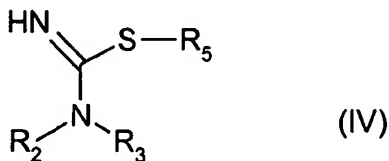
Synthesis route A

Step 1 of route A

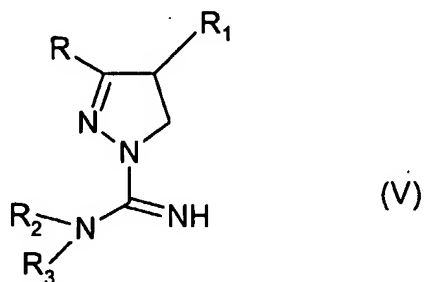
Reaction of a compound having formula (III)



with a compound having formula (IV)



wherein R_5 represents a lower alkyl group, such as for example 2-methyl-2-thiopseudourea, or with a suitable salt form thereof in the presence of a base. This reaction gives a 4,5-dihydro-1H-pyrazole-1-carboxamidine derivative having formula (V)



wherein the symbols have the meanings as mentioned above. Compounds having formula (V) wherein R, R_1 , R_2 and R_3 have the meaning as described herein above for compound (I) are new.

Alternatively, a compound having formula (III) is reacted with a so-called guanylyating agent. Examples of such guanylyating agents are 1H-pyrazole-1-carboxamidine and its salts (for example the hydrochloride salt) and 3,5-dimethyl-1H-pyrazole-1-carboxamidine and its salts (for example the nitrate salt) and the like. This reaction gives a carboxamidine derivative having formula (V).

Alternatively, a compound having formula (III) is reacted with a so-called protected guanylyating agent. Examples of such protected guanylyating agents are N-(benzyloxycarbonyl)-1H-pyrazole-1-carboxamidine, N-(*tert*-butoxycarbonyl)-1H-pyrazole-1-carboxamidine and N,N'-bis-(*tert*-butoxycarbonyl)-1H-pyrazole-1-carboxamidine and the like. This reaction gives after deprotection a compound having formula (V).

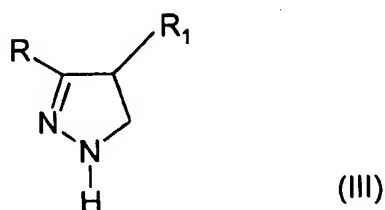
15 Step 2 of route A

The compound having formula (V) is reacted with an optionally substituted compound of the formula $R_4\text{-SO}_2\text{X}$, wherein R_4 has the above mentioned meaning and X represents a halogen atom. This reaction is preferably carried out in the presence of a base, such as triethylamine in an aprotic solvent, such as acetonitrile.

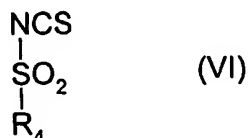
Synthesis route A1

Step 1 of route A1

25 Reaction of a compound having formula (III)



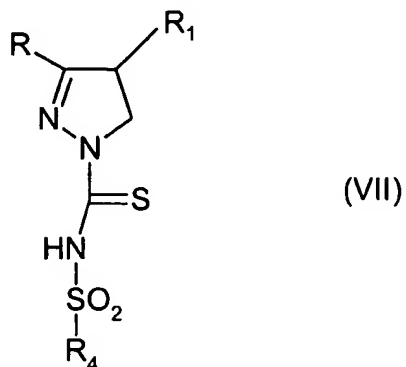
with a thioisocyanate derivative having formula (VI) .



This reaction is preferably carried out in an inert organic solvent, such as for example acetonitrile.

6

This reaction gives a thiocarboxamide derivative having formula (VII). Compounds having formula (VII) wherein R, R₁ and R₄ have the meaning as described herein above for compound (I) are new.



5 Step 2 of route A1

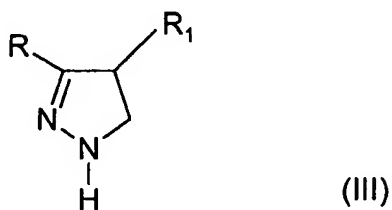
Reaction of a compound having formula (VII) with an amine in the presence of a mercury(II) salt, such as for example HgCl₂, gives a compound having formula (I). This reaction is preferably carried out in a polar organic solvent, such as for example acetonitrile.

10

Synthesis route A2

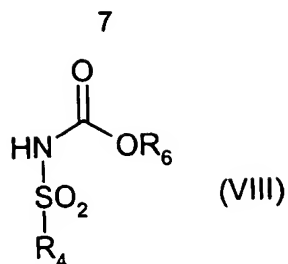
Step 1 of route A2

Reaction of a compound having formula III



15

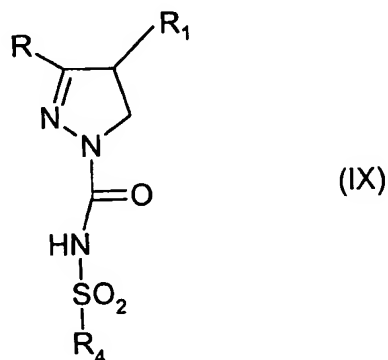
with a carbamate ester derivative having formula (VIII).



wherein R₆ represents a lower alkyl group, for example methyl.

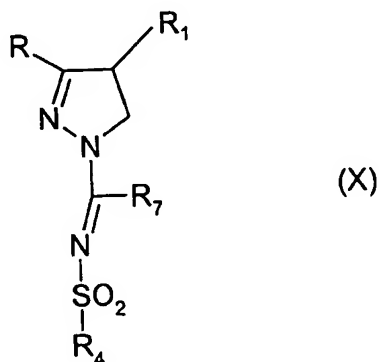
This reaction is preferably carried out in an inert organic solvent, such as for example 1,4-dioxane.

5 This reaction gives a 4,5-dihydropyrazole-1-carboxamide derivative having formula (IX). Compounds having formula (IX) wherein R, R₁ and R₄ have the meaning as described herein above for compound (I) are new.



Step 2 of route A2

10 Reaction of a compound having formula (IX) with a halogenating agent, such as for example PCl₅, gives a 4,5-dihydropyrazole-1-carboximidoyl halogenide derivative having formula (X).



wherein R_7 represents a halogen atom, such as for example chloro. This reaction is preferably carried out in an inert organic solvent, such as for example chlorobenzene.

Compounds having formula (X) wherein R , R_1 and R_4 have the meaning as described herein above for compound (I) and wherein R_7 represents a halogen atom are new.

Step 3 of route A2

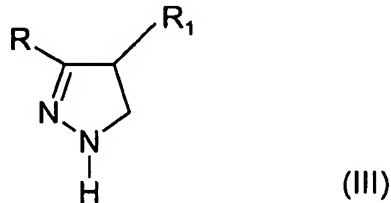
Reaction of a compound having formula (X) with an amine gives a compound having formula (I).

This reaction is preferably carried out in an inert organic solvent, such as for example dichloromethane.

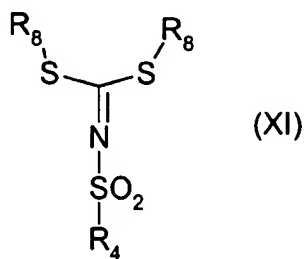
Synthesis route A3

Step 1 of route A3

Reaction of a compound having formula III

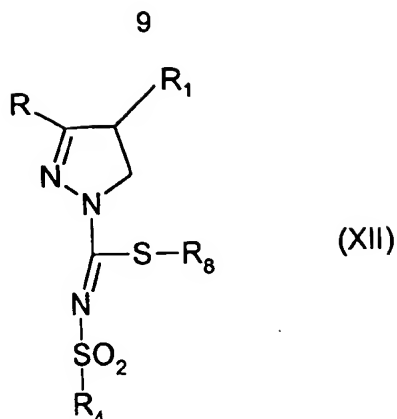


with a dithioimidocarbonic ester derivative having formula (XI) .



wherein R_8 represents a C_{1-3} alkyl group.

This reaction is preferably carried out in a polar organic solvent, such as for example acetonitrile.



This reaction gives a carboximidothioic ester derivative having formula (XII).

Compounds having formula (XII) wherein R, R₁ and R₄ have the meaning as described herein above for compound (I) and wherein R₈ represents a C₁₋₃ alkyl group are new.

Step 2 of route A3

Reaction of a compound having formula (XII) with an amine gives a compound having formula (I).

This reaction is preferably carried out in a polar organic solvent, such as for example methanol.

Example I

3-(4-Chlorophenyl)-4,5-dihydro-N-((4-fluorophenyl)sulfonyl)-4-phenyl-1H-pyrazole-1-carboxamide

Part A: A stirred mixture of 3-(4-chlorophenyl)-4,5-dihydro-4-phenyl-1H-pyrazole (5.13 gram, 20.0 mmol), 2-methyl-2-thiopseudourea hydroiodide (5.00 gram, 23.0 mmol) and pyridine (10 ml) is heated at 110 °C for 1 hour. After one night standing at room temperature diethyl ether is added and the precipitate is collected by filtration. This precipitate is washed three times with diethyl ether portions to afford a solid (9 gram). Melting point: ~230 °C. This solid is dissolved in methanol (20 ml). To the resulting solution is successively added a 2N sodium hydroxide solution (12 ml) and water (200 ml). The formed precipitate is collected by filtration, washed two times with diethyl ether and successively with diisopropyl ether. The resulting solid is dried *in vacuo* to yield 3-(4-chlorophenyl)-4,5-dihydro-4-phenyl-1H-pyrazole-1-carboxamide (5.1 gram, 88 % yield). Melting point: 187-189 °C.

Part B: To a stirred mixture of 3-(4-chlorophenyl)-4,5-dihydro-4-phenyl-1H-pyrazole-1-carboxamide (0.50 gram, 1.68 mmol) and 4-fluorophenylsulfonyl

chloride (0.34 gram, 1.75 mmol) in acetonitrile (10 ml) is added N,N-dimethyl-4-aminopyridine (0.020 gram, 0.175 mmol) and triethylamine (1 ml). The resulting solution is stirred at room temperature for 30 minutes. After addition of a 2N sodium hydroxide solution and extraction with ethylacetate (400 ml), the ethylacetate layer is concentrated *in vacuo*. The resulting crude residue is further purified by means of flash chromatography (petroleum ether/diethyl ether = 1/1 (v/v), followed by ethylacetate). Subsequent concentration *in vacuo* affords solid 3-(4-chlorophenyl)-4,5-dihydro-N-((4-fluorophenyl)sulfonyl)-4-phenyl-1H-pyrazole-1-carboxamide (0.55 gram, 72 % yield). Melting point: 214-215 °C

In an analogous manner the compounds having formula (I) listed below have been prepared:

4,5-Dihydro-N-((4-fluorophenyl)sulfonyl)-3-(4-methoxyphenyl)-4-(4-methoxyphenyl)-1H-pyrazole-1-carboxamide: Melting point: 155-156 °C

4,5-Dihydro-3-(4-methoxyphenyl)-4-(4-methoxyphenyl)-N-((4-methoxyphenyl)sulfonyl)-1H-pyrazole-1-carboxamide: Melting point: 148-150 °C

3-(4-Chlorophenyl)-4,5-dihydro-4-phenyl-N-((2,4,6-trimethylphenyl)sulfonyl)-1H-pyrazole-1-carboxamide: Melting point: 221-222 °C

Example II

N',N'-Dimethyl-N²-((4-chlorophenyl)sulfonyl)-3-(4-chlorophenyl)-4,5-dihydro-4-phenyl-1H-pyrazole-1-carboxamide

Part A: A stirred mixture of 3-(4-chlorophenyl)-4,5-dihydro-4-phenyl-1H-pyrazole (12.0 gram, 46.8 mmol), [(4-chlorophenyl)sulfonyl]dithioimidocarbonic acid dimethyl ester (CAS: 13068-12-7) (9.20 gram, 31.1 mmol) and triethylamine (15 ml) in acetonitrile (200 ml) is heated at reflux temperature for 20 hours. An additional portion of 3-(4-chlorophenyl)-4,5-dihydro-4-phenyl-1H-pyrazole (12.0 gram, 46.8 mmol) is added and the resulting mixture is heated at reflux temperature for another 16 hours. After concentration *in vacuo*, dichloromethane is added and the resulting solution is washed twice with water and dried over anhydrous Na₂SO₄. After filtration and evaporation *in vacuo* the residue is further purified by flash chromatography (diethyl ether/ petroleum ether = 1/1 (v/v)) to give 3-(4-chlorophenyl)-N-((4-chlorophenyl)sulfonyl)-4,5-dihydro-4-phenyl-1H-pyrazole-1-carboximidothioic acid methyl ester (12.5 gram, 80% yield based on [(4-chlorophenyl)sulfonyl]dithioimidocarbonic acid dimethyl ester) as an amorphous solid.

Part B: To a stirred mixture of 3-(4-chlorophenyl)-N-((4-chlorophenyl)sulfonyl)-4,5-dihydro-4-phenyl-1H-pyrazole-1-carboximidothioic acid methyl ester (4.20 gram, 8.30 mmol) in methanol (75 ml) is added dimethylamine (10 ml) and dichloromethane (75 ml) and the resulting solution is stirred at room temperature for 6 hours. Evaporation *in vacuo* and subsequent flash chromatographic purification (diethyl ether/ petroleum ether = 1/1 (v/v), followed by diethyl ether) gives a solid which is further purified by recrystallisation from diisopropyl ether to yield N¹-dimethyl-N²-((4-chloro-phenyl)sulfonyl)-3-(4-chlorophenyl)-4,5-dihydro-4-phenyl-1H-pyrazole-1-carboxamidine (2.63 gram, 63 % yield). Melting point: 182 °C.

In an analogous manner the compounds having formula (I) listed below have been prepared:

N-Methyl-N'-((4-chlorophenyl)sulfonyl)-3-(4-chlorophenyl)-4,5-dihydro-4-(3-pyridyl)-1H-pyrazole-1-carboxamidine. Melting point: 101-105 °C.

N-Methyl-N'-((4-chlorophenyl)sulfonyl)-3-(4-chlorophenyl)-4,5-dihydro-4-(4-pyridyl)-1H-pyrazole-1-carboxamidine. Melting point: 112-115 °C.

Example III

N-Methyl-N'-((4-chlorophenyl)sulfonyl)-3-(4-chlorophenyl)-4,5-dihydro-4-phenyl-1H-pyrazole-1-carboxamidine

Part A: To a solution of N-((4-chlorophenyl)sulfonyl)carbamic acid methyl ester (CAS: 34543-04-9) (2.99 gram, 12.0 mmol) and pyridine (4 ml) in 1,4-dioxane (20 ml) is added 3-(4-chlorophenyl)-4,5-dihydro-4-phenyl-1H-pyrazole (3.39 gram, 13.2 mmol) and the resulting mixture is stirred for 4 hours at 100 °C. After concentration *in vacuo* the residue is dissolved in dichloromethane, successively washed with water, 1N HCl and water, dried over anhydrous Na₂SO₄, filtered and concentrated *in vacuo* to a volume of 20 ml. Methyl-*tert*-butyl ether (60 ml) is added and the resulting solution is concentrated to a volume of 20 ml. The formed crystals are collected by filtration and recrystallised from methyl-*tert*-butyl ether to give 3-(4-chlorophenyl)-N-((4-chlorophenyl)sulfonyl)-4,5-dihydro-4-phenyl-1H-pyrazole-1-carboxamide (4.75 gram, 76 % yield) Melting point: 211-214 °C.

Part B: A mixture of 3-(4-chlorophenyl)-N-((4-chlorophenyl)sulfonyl)-4,5-dihydro-4-phenyl-1H-pyrazole-1-carboxamide (3.67 gram, 7.75 mmol) and phosphorus pentachloride (1.69 gram, 8.14 mmol) in chlorobenzene (40 ml) is heated at reflux for 1 hour. After thorough concentration *in vacuo*, the formed N-((4-chlorophenyl)sulfonyl)-3-(4-chlorophenyl)-4,5-dihydro-4-phenyl-1H-pyrazole-1-

carboximidoyl chloride is suspended in dichloromethane and reacted with cold methylamine (1.5 ml). After stirring at room temperature for 1 hour, the mixture is concentrated *in vacuo*. The residue is crystallised from diethyl ether to give

5 N-methyl-N'-((4-chlorophenyl)sulfonyl)-3-(4-chlorophenyl)-4,5-dihydro-4-phenyl-1H-pyrazole-1-carboxamide (2.29 gram, 61 % yield). Melting point: 96-98 °C (dec.).

In an analogous manner the compounds having formula (I) listed below have been prepared:

- 10 N-Methyl-N'-((3-chlorophenyl)sulfonyl)-3-(4-chlorophenyl)-4,5-dihydro-4-phenyl-1H-pyrazole-1-carboxamide. Melting point: 156-160 °C.
- N-Propyl-N'-((4-fluorophenyl)sulfonyl)-3-(4-chlorophenyl)-4,5-dihydro-4-phenyl-1H-pyrazole-1-carboxamide. Melting point: 129-138 °C.
- 15 N-(2-Propyl)-N'-((4-fluorophenyl)sulfonyl)-3-(4-chlorophenyl)-4,5-dihydro-4-phenyl-1H-pyrazole-1-carboxamide. Melting point: 110-112 °C.
- N-(2-Propyl)-N'-((4-chlorophenyl)sulfonyl)-3-(4-pyridyl)-4,5-dihydro-4-phenyl-1H-pyrazole-1-carboxamide. Melting point: Amorphous.
- N¹-Ethyl-N¹-methyl-N²-((4-chlorophenyl)sulfonyl)-3-(4-chlorophenyl)-4,5-dihydro-4-phenyl-1H-pyrazole-1-carboxamide. Melting point: 184 °C.
- 20 N¹-Ethyl-N¹-methyl-N²-((4-fluorophenyl)sulfonyl)-3-(4-chlorophenyl)-4,5-dihydro-4-phenyl-1H-pyrazole-1-carboxamide. Melting point: 173-176 °C.
- N¹,N¹-Dimethyl-N²-((4-(trifluoromethyl)phenyl)sulfonyl)-3-(4-chlorophenyl)-4,5-dihydro-4-phenyl-1H-pyrazole-1-carboxamide. Melting point: 195-196 °C.
- N¹,N¹-Dimethyl-N²-((3-methylphenyl)sulfonyl)-3-(4-chlorophenyl)-4,5-dihydro-4-phenyl-1H-pyrazole-1-carboxamide. Melting point: 195-198 °C.
- 25 N¹,N¹-Dimethyl-N²-((3-methoxyphenyl)sulfonyl)-3-(4-chlorophenyl)-4,5-dihydro-4-phenyl-1H-pyrazole-1-carboxamide. Melting point: 204-206 °C.
- N-Ethyl-N'-((4-chlorophenyl)sulfonyl)-3-(4-chlorophenyl)-4,5-dihydro-4-phenyl-1H-pyrazole-1-carboxamide. Melting point: Amorphous.
- 30 N-Dimethylamino-N'-((4-chlorophenyl)sulfonyl)-3-(4-chlorophenyl)-4,5-dihydro-4-phenyl-1H-pyrazole-1-carboxamide. Melting point: 155-159 °C.
- N-Methyl-N'-((4-(trifluoromethyl)phenyl)sulfonyl)-3-(4-chlorophenyl)-4,5-dihydro-4-phenyl-1H-pyrazole-1-carboxamide. Melting point: Amorphous.
- N¹,N¹-Dimethyl-N²-((2-methylphenyl)sulfonyl)-3-(4-chlorophenyl)-4,5-dihydro-4-phenyl-1H-pyrazole-1-carboxamide. Melting point: 148-151 °C.
- 35 N-Methyl-N'-((2,4-difluorophenyl)sulfonyl)-3-(4-chlorophenyl)-4,5-dihydro-4-phenyl-1H-pyrazole-1-carboxamide. Melting point: 85 °C.

Example IV**(-)-(4S)-N-methyl-N'-((4-chlorophenyl)sulfonyl)-3-(4-chlorophenyl)-4,5-dihydro-4-phenyl-1H-pyrazole-1-carboxamide**

5 (-)-(4S)-N-Methyl-N'-((4-chlorophenyl)sulfonyl)-3-(4-chlorophenyl)-4,5-dihydro-4-phenyl-1H-pyrazole-1-carboxamide (7.16 gram, 0.0147 mol) ($[\alpha]^{25}_D$ = -150°, c = 0.01, MeOH) (melting point: 169-170 °C) was obtained via chiral chromatographic separation of racemic N-methyl-N'-((4-chlorophenyl)sulfonyl)-3-(4-chlorophenyl)-4,5-dihydro-4-phenyl-1H-pyrazole-1-carboxamide (18 gram, 0.037 mol) using a Chiralpak AD, 20 μ m chiral stationary phase. The mobile phase consisted of a mixture of hexane/ethanol (80/20 (v/v)) and 0.1 % ammonium hydroxide (25 % aqueous solution).

15 In an analogous manner the optically pure compounds listed below have been prepared from the corresponding racemates:

(-)-(4S)-N-Ethyl-N'-((4-chlorophenyl)sulfonyl)-3-(4-chlorophenyl)-4,5-dihydro-4-phenyl-1H-pyrazole-1-carboxamide: ($[\alpha]^{25}_D$ = -126 °, c = 0.01, CHCl₃); Melting point: 172-175 °C. Stationary phase: Chiralcel OD. Mobile phase: A mixture of heptane/2-propanol (85/15 (v/v)).

20 (-)-(4S)-N-Dimethylamino-N'-((4-chlorophenyl)sulfonyl)-3-(4-chlorophenyl)-4,5-dihydro-4-phenyl-1H-pyrazole-1-carboxamide: ($[\alpha]^{25}_D$ = -132 °, c = 0.01, CHCl₃); Melting point: 218-224 °C. Stationary phase: Chiralcel OD. Mobile phase: A mixture of heptane/2-propanol (85/15 (v/v)).

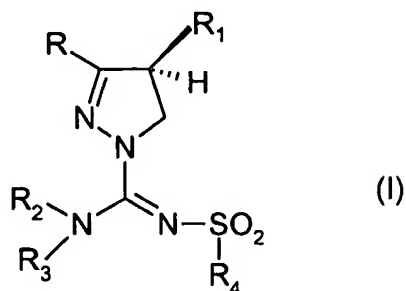
25 (-)-(4S)-N-Methyl-N'-((4-(trifluoromethyl)phenyl)sulfonyl)-3-(4-chlorophenyl)-4,5-dihydro-4-phenyl-1H-pyrazole-1-carboxamide: ($[\alpha]^{25}_D$ = -131 °, c = 0.01, CHCl₃); Melting point: 157-160 °C. Stationary phase: Chiralcel OD. Mobile phase: A mixture of heptane/2-propanol (85/15 (v/v)).

(-)-(4S)-N¹,N¹-Dimethyl-N²-((2-methylphenyl)sulfonyl)-3-(4-chlorophenyl)-4,5-dihydro-4-phenyl-1H-pyrazole-1-carboxamide: ($[\alpha]^{25}_D$ = -88 °, c = 0.01, MeOH); Melting point: Amorphous. Stationary phase: Chiralpak AD. Mobile phase: Ethanol.

(-)-(4S)-N-Methyl-N'-((2,4-difluorophenyl)sulfonyl)-3-(4-chlorophenyl)-4,5-dihydro-4-phenyl-1H-pyrazole-1-carboxamide: ($[\alpha]^{25}_D$ = -129 °, c = 0.01, MeOH); Melting point: Amorphous. Chiralpak AD. Mobile phase: Methanol.

Claims

1. The enantiomer having S configuration at the 4-position of their 4,5-dihydro pyrazole ring of a compound of formula (I)



wherein

- R and R₁ are the same or different and represent 3-pyridyl or 4-pyridyl, or phenyl which may be substituted with halogen or methoxy,
- R₂ and R₃ are the same or different and represent hydrogen, alkyl (1-3 C) or dimethylamino
- R₄ represents phenyl which may be substituted with 1, 2 or 3 substituents selected from the group halogen atoms, trifluoromethyl, methoxy and alkyl (1-3 C)

and tautomers, prodrugs and salts thereof.

2. A compound having formula (I) as claimed in claim 1, wherein R is the group 4-chlorophenyl, R₁ is phenyl, R₂ is hydrogen, R₃ is methyl and R₄ represents 4-chlorophenyl, and salts thereof.
3. A pharmaceutical composition containing at least one compound as claimed in claim 1 as an active component.
4. A method of preparing pharmaceutical compositions characterized in that a compound as claimed in claim 1 is brought in a form suitable for administration.
5. Process for the preparation of compounds having formula I, characterized in that the racemic mixture of a compound having formula I is separated into the levorotatory and the dextrorotatory enantiomers.

- 5 6. A method of treating psychiatric disorders such as psychosis, anxiety, depression, attention deficits, memory disorders and appetite disorders, obesity, neurological disorders such as Parkinson's disease, dementia, dystonia, Alzheimer's disease, epilepsy, Huntington's disease, Tourette's syndrome, ischaemia, pain and other CNS-diseases involving cannabinoid neurotransmission, characterized in that a compound as claimed in claim 1 is used.
- 10 7. A method of treating gastrointestinal disorders involving cannabinoid neurotransmission, characterized in that a compound as claimed in claim 1 is used.
- 15 8. A method of treating cardiovascular disorders involving cannabinoid neurotransmission, characterized in that a compound as claimed in claim 1 is used.

INTERNATIONAL SEARCH REPORT

Internat Application No

PCT/EP 02/03079

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 C07D231/06 C07D401/04 A61K31/415 A61P25/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C07D A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data, PAJ, BEILSTEIN Data, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	PERTWEE, R. G.: "Pharmacology of Cannabinoid Receptor Ligands" CURRENT MED. CHEM., vol. 6, 1999, pages 635-664, XP000923352 cited in the application Pages 657-659, chapter "Diarylpyrazoles"; and page 641, figure 5.	1-5
A	US 5 624 941 A (BARTH, F. ET AL.) 29 April 1997 (1997-04-29) Claim 1, formula (I); column 26, lines 27-65; column 28, lines 41-59.	1-5
A	US 4 070 365 A (VAN DAALEN, J. J. ET AL.) 24 January 1978 (1978-01-24) Claim 1; abstract.	1-5



Further documents are listed in the continuation of box C.



Patent family members are listed in annex.

* Special categories of cited documents:

- *A* document defining the general state of the art which is not considered to be of particular relevance
- *E* earlier document but published on or after the international filing date
- *L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- *O* document referring to an oral disclosure, use, exhibition or other means
- *P* document published prior to the international filing date but later than the priority date claimed

- *T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- *X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- *Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- *Z* document member of the same patent family

Date of the actual completion of the international search

18 June 2002

Date of mailing of the international search report

25/06/2002

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2
 NL - 2280 HV Rijswijk
 Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,
 Fax: (+31-70) 340-3016

Authorized officer

Weisbrod, T

INTERNATIONAL SEARCH REPORT

Intern

ial Application No

PCT/EP 02/03079

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	EP 0 173 323 A (BAYER AG) 5 March 1986 (1986-03-05) Abstract; claim 1; page 32, example 1. -----	1-5

INTERNATIONAL SEARCH REPORT

information on patent family members

Internat'l Application No

PCT/EP 02/03079

Patent document cited in search report		Publication date	Patent family member(s)		Publication date
US 5624941	A	29-04-1997	FR	2692575 A1	24-12-1993
			FR	2713224 A1	09-06-1995
			FR	2713225 A1	09-06-1995
			AT	149489 T	15-03-1997
			AU	4143893 A	06-01-1994
			BR	1100409 A3	13-10-1999
			BR	9302435 A	11-01-1994
			CA	2098944 A1	24-12-1993
			CZ	9301172 A3	16-03-1994
			DE	69308395 D1	10-04-1997
			DK	576357 T3	15-09-1997
			EP	0576357 A1	29-12-1993
			ES	2101258 T3	01-07-1997
			FI	932891 A	24-12-1993
			GR	3023535 T3	29-08-1997
			HU	64526 A2	28-01-1994
			IL	106099 A	15-07-1998
			JP	3238801 B2	17-12-2001
			JP	6073014 A	15-03-1994
			MX	9303664 A1	31-01-1994
			NO	932296 A	27-12-1993
			NZ	247961 A	28-08-1995
			RU	2119917 C1	10-10-1998
			SK	65493 A3	02-02-1994
			ZA	9304511 A	22-02-1994
			AT	154012 T	15-06-1997
			AU	685518 B2	22-01-1998
			AU	7899994 A	15-06-1995
			BR	1100984 A3	14-03-2000
			CA	2136893 A1	21-06-1995
			CN	1110968 A ,B	01-11-1995
			CZ	9403016 A3	14-06-1995
			DE	69403614 D1	10-07-1997
			DE	69403614 T2	22-01-1998
			DK	656354 T3	29-12-1997
			EP	0656354 A1	07-06-1995
			ES	2105575 T3	16-10-1997
			FI	945690 A	03-06-1995
			GR	3024470 T3	28-11-1997
			HK	1000599 A1	09-04-1998
			HU	71498 A2	28-11-1995
			IL	111719 A	28-10-1999
			JP	3137222 B2	19-02-2001
			JP	7309841 A	28-11-1995
			JP	2001026541 A	30-01-2001
			NO	944625 A	06-06-1995
			NZ	270025 A	26-09-1995
			PL	306067 A1	12-06-1995
			RU	2141479 C1	20-11-1999
			SG	68570 A1	20-06-2000
US 4070365	A	24-01-1978	NL	7409433 A	14-01-1976
			AR	223449 A1	31-08-1981
			AT	359775 B	25-11-1980
			AT	508277 A	15-04-1980
			AT	342585 B	10-04-1978
			AT	529175 A	15-08-1977
			AU	501280 B2	14-06-1979

INTERNATIONAL SEARCH REPORT

information on patent family members

International Application No

PCT/EP 02/03079

Patent document cited in search report		Publication date	Patent family member(s)	Publication date		
US 4070365	A		AU 8285075 A	13-01-1977		
			BE 831232 A1	12-01-1976		
			BR 7504413 A	06-07-1976		
			CA 1075242 A1	08-04-1980		
			CH 624675 A5	14-08-1981		
			CS 188962 B2	30-03-1979		
			DD 122775 A5	05-11-1976		
			DE 2529689 A1	29-01-1976		
			DK 310975 A , B,	13-01-1976		
			EG 11880 A	30-09-1978		
			ES 439292 A1	16-02-1977		
			FR 2277827 A1	06-02-1976		
			GB 1514285 A	14-06-1978		
			HU 178320 B	28-04-1982		
			IE 41836 B1	09-04-1980		
			IL 47676 A	31-01-1979		
			IT 1044358 B	20-03-1980		
			JP 1368569 C	11-03-1987		
			JP 51041358 A	07-04-1976		
			JP 61023162 B	04-06-1986		
			OA 5057 A	31-12-1980		
			PL 193676 A1	17-07-1978		
			SE 419644 B	17-08-1981		
			SE 7507868 A	13-01-1976		
			US 4156007 A	22-05-1979		
			YU 176475 A1	30-06-1982		
			ZA 7504203 A	23-02-1977		
		EP 0173323	A	05-03-1986	DE 3431926 A1	06-03-1986
					AU 4665285 A	06-03-1986
					BR 8504157 A	24-06-1986
					CA 1218366 A1	24-02-1987
					DD 237782 A5	30-07-1986
	DK 392985 A			01-03-1986		
	EP 0173323 A1			05-03-1986		
	ES 546559 D0			01-03-1986		
	ES 8604942 A1			01-08-1986		
	GR 852092 A1			30-12-1985		
	HU 41210 A2			28-04-1987		
	JP 61060684 A			28-03-1986		
	ZA 8506593 A			30-04-1986		